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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,049	04/01/2002	William Thomas Melvin	0380-P02753US0	4396

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 10/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/009,049	MELVIN ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,10-19,21-24,27-29 and 31-38* is/are pending in the application.

4a) Of the above claim(s) *12-19,22-24,27-29,33-35 and 37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,10,11,21,31,32,36 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 7/28/03, is acknowledged.

2. Claims 1, 4, 10-19, 21-24, 27-29 and 31-38 are pending.

3. Claims 12-19, 22-24, 27-29, 33-35 and 37 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 1, 4, 10-11, 21, 31, 32, 36 and 38 are under consideration in the instant application as they read on a peptide of SEQ ID NO: 1-3, variants, fragments and a fusion peptide.

5. Claim 4 is objected to because of the following informalities: the word "fo" recited in claim 4, line 8 is misspelled. Correction is required.

6. In view of the amendment filed on 7/28/03, only the following New Grounds of Rejections are set forth herein.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 4, 31-32 and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 is indefinite in the recitation "said peptide being between 8 to 14 amino acids in length" because it is unclear how a 8 to 14 amino acid peptide would be a 15 amino acid peptide (SEQ IDNO:1-3).

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 4, 10-11, 21, 31, 32, 36 and 38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The phrase "composed of an amino acid sequence" claimed in claim 1, line 1, the phrase "which composed of a" claimed in claims 4 and 38, line 1 and line 1-2, respectively and the phrase "said

peptide being between 8 to 14 amino acids in length" claimed in claim 4, line 7, represent a departure from the specification and the claims as originally filed.

Applicant's amendment filed 7/28/03 points to the specification at page 6, line 20 for support for the newly added limitations "composed of an amino acid sequence" as claimed in claim 1, "which composed of a" as claimed in claims 4 and 38 and "said peptide being between 8 to 14 amino acids in length" as claimed in claim 4. However, the specification does not provide a clear support of "composed of an amino acid sequence", "which composed of a" and "said peptide being between 8 to 14 amino acids in length". Examiner notes that the specification on page 6, line 20, discloses the fragment to be 8-15 or 8-11 amino acids in length. Applicant cites In re Blaser, 194, U.S.P.Q (CCPA 1997) to support that "disclosure of broad range provides support for narrower included range". However, In re Blaser, the disclosure of molecular weight ranges of 40,000-130,000 and 60,000-90,000 was sufficient to establish the 60,000-130,000 range. However, in the instant application, Applicants fail to disclose the support for any fragment between 8-14 amino acids in length. The instant claims now recite limitations which were not clearly disclosed in the specification and claims as originally filed.

10. In view of the amendment filed on 7/28/03, only the following rejections remained.

11. Claims 1, 4, 10-11, 21, 31, 32, 36 and 38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a peptide of SEQ ID NO:1-3 that is capable of modulating a fibrin fragment E activity, does not reasonably provide **enablement** for any peptide "composed of" any amino acids sequence selected from the group consisting of SEQ ID NO:1-3; any peptide which is "composed of" any fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-3, said peptide being between 8 to 14 amino acids in length, wherein said peptide is capable of modulating a fibrin fragment E activity in claim 4, Any fusion peptide which comprises a first portion "having" the amino acid sequence of any peptide according to claim 1 and a second portion, attached to the N-or C-terminus of the first portion, which comprises a sequence of amino acids not naturally contiguous to the first portion, said second portion comprising a membrane translation sequence in claim 11, a composition comprising any peptide according to claim 1 in association with a pharmaceutically acceptable carrier or diluent in claim 21, any fragment of a peptide according to claim 4, wherein said activity is stimulation of cell proliferation or angiogenesis in claim 31, any fusion peptide which comprises a first portion "having" the amino acid sequence of any fragment of a peptide according to claim 4 and a second portion , attached to the N-or C-terminus of the first portion, which comprises a sequence of amino acids not naturally contiguous to the first portion, said second portion comprising a membrane translocation sequence in claim 32, any composition comprising any fragment of a peptide according to claim 4, in association with a pharmaceutically acceptable carrier or diluent in claim 36; any peptide which is "composed of a variant of an amino acid sequence selected from the group consisting of SEQ ID NO: 1-3, said peptide having one or two conservative amino acid substitutions with respect to said amino acid sequence, wherein the peptide is capable of modulating a fibrin fragment E activity in claim 38. The specification does not enable any person skilled in the art to which it pertains, or with which

it is most nearly connected, to make and or use the invention commensurate in scope with this claim for the same reasons set forth in the previous Office Action, mailed 03/24/03.

Further, the teams "composed of" and "having" recited in claims 1, 4, 11, 32 and 38 are open ended, they would open up the claims to include additional undisclosed amino acids at either or both N- or C- termini of SEQ ID NO: 1-3 or fragments, variants thereof. Such a recitation does not require that the full length sequence set forth in SEQ ID NO:1-3; but rather encompasses any 8-14 amino acid sequence comprising either any fragment of SEQ ID NO:1-3 *or variant thereof.* However, the specification does not appear to have provided sufficient guidance as to which subsequences of SEQ ID NO:1-3 would share the function of modulating a fibrin fragment E activity. Neither does the specification appear to have provided any working examples of any functional fragments or variants. Further, claim 4 reads on at least two amino acid fragment within 8-14 amino acid sequence. However, the specification does not disclose the other amino acids outside the at least 2 amino acids fragment that is derived from SEQ ID NO: 1-3. Thus it would require undue experimentation of the skilled artisan to determine which subsequences or variants of SEQ ID NO:1-3 would have the function of the full length molecule.

It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions can result in substantially different biological activities. Because of the lack of sufficient guidance and predictability in determining which modifications would lead to the stimulation of cell proliferation or angiogenesis and that the relationship between the peptide and its activity was not well understood. It would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of modulating a fibrin fragment E activity. Without sufficient guidance, the changes which can be made in the structure of "a peptide" and still provide modulating a fibrin fragment E activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Applicant's arguments, filed 7/28/03, have been fully considered, but have not been found convincing

Applicant traverse the rejection on the ground that in terms of making further variants and fragments, it is clear that this is well within the capabilities of those skilled in the art. Further, the terms of the biological activity of the variants and fragments of this invention, there are no well founded reasons to doubt that such variants will share the biological activity of the recited sequences. The Examiner agrees in the context of how to make any variants or fragments, however a person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences. There is insufficient guidance to direct a person of skill in the art to select particular sequences or sequence lengths as essential for modulating a fibrin fragment E activity. Without detailed direction as to which amino acid sequences are essential to the function of the peptide, a person of skill in the art would not be able to determine without undue experimentation which of the plethora of amino acid sequences encompassed by the instant claims would share the ability to

bind fibrinogen E, other than the amino acid of SEQ ID NO:1-3. The specification discloses only four species, yet claim any 8-14 amino acid portion composed of any fragment of SEQ ID NO: 1-3. No active fragments, analogs, derivatives, etc. have been provided, and the claims cannot be considered enabled for anything other than SEQ ID NO:1-3.

However, it is recognized in the prior art that the function of a protein depends on the sequence of its amino acids in a certain pattern, conformation of the protein due to the amino acid sequence and the functional properties of the different parts of the protein. The claims as written encompass a broad genus of polypeptides with an unlimited number of possibilities with regard to the length of the polypeptide sequence. Further, the specification does not teach and provide sufficient guidance as to which amino acid of the disclosed 15 amino acids would have been altered such that the resultant polypeptide would have retained the function of modulating a fibrin fragment E activity. In addition variation of the 15 amino acids ($15\ X19^{15}$) provide a range of activities, not all which are necessarily predictive of modulating a fibrin fragment E activity. Therefore, absent the ability to predict which of these polypeptides would function as claimed for one of skill in the art to practice the invention as claimed would required a level of experimentation that is excessive and undue.

Applicant submits that examples 2 and 4 provide sufficient direction as to how to use any peptide variant of this invention, such that the desired effect can be achieved. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the peptide which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. In addition, this further characterization, however, is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. In order to satisfy 112, first paragraph, the specification has to teach how to make and use the polypeptides of the invention not how to identify and screen for peptide of the invention.

Applicant submits that while some experimentation may be necessary in carrying out the present invention, the amount of experimentation involved certainly cannot be considered excessive or undue in light of the disclosure provided by applicant herein.

Applicant's arguments have been considered but are not found to be persuasive because the broad brush discussion of making and screening for fragments and variants does not constitute a disclosure of a representative number of members. No such variants or fragments were made or shown to have activity. Only the peptides of SEQ ID NO: 1-3 are disclosed. The specification's general discussion of making and screening for fragments and variants constitutes an invitation to experiment by trial and error.

Applicant argues regarding Burgess et al that the fact that such a radical change in what was already identified as a key residue has any bearing on the present case.

Applicant argues regarding Lazar et al that generally those skilled in the art do not expect that conservative substitutions will not have profound effects on activity. The fact that there are surprising exceptions sometimes does not mean that this is not a reasonable expectation.

Applicant argues that Kogan et al confirms that sometimes what might be predicted, does not happen. Applicant submits that the fact that there are exceptions to the generally accepted rule that conservative substitutions will not profoundly affect activity does not mean that it is not a reasonable rule to follow. Moreover, there is nothing in this reference to suggest the authors were discussing biological effects in general, rather than E-selectin in particular.

Applicant submits that Bowie [Burgess] et al do not contradicts the view that it is possible that some conservative "variants" of the recited sequences may surprisingly fall out side the scope of the claim. However, this possibility should not per se be justification for asserting that the claimed subject matter is not itself enabled by the specification.

Contrary to Applicant assertions, these references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Furthermore, the specification fails to teach what deletions, insertions, substitutions and mutations of the disclosed sequence can be tolerated that will allow the peptide to function as claimed. While it is known that many amino acid substitutions are possible in any given peptide, the position within the peptide's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the structure/function relationship.

Consequently, without additional guidance in the specification, and the dearth of information in the art, for one of skill in the art to practice the invention as claimed, would require experimentation that is excessive and undue. The amount of guidance or direction needed to enable an invention is inversely related to the mount of knowledge in the state of the art as well as the predictability in the art (In re Fisher, 427 F.2d 833, 839, 166 USPQ 18,24 (CCPA 1970)).

12. Claims 1, 4, 10-11, 21, 31, 32, 36 and 38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention claim for the same reasons set forth in the previous Office Action, mailed 03/24/03.

Applicant is in possession of a peptide of SEQ ID NO:1-3 that is capable of modulating a fibrin fragment E activity.

Applicant is not in possession of any amino acids sequence selected from the group consisting of SEQ ID NO:1-3; any peptide which is "composed of" any fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-3, said peptide being between 8 to 14 amino acids in length, wherein said peptide is capable of modulating a fibrin fragment E activity in

claim 4, Any fusion peptide which comprises a first portion "having" the amino acid sequence of any peptide according to claim 1 and a second portion, attached to the N-or C-terminus of the first portion, which comprises a sequence of amino acids not naturally contiguous to the first portion, said second portion comprising a membrane translation sequence in claim 11, a composition comprising any peptide according to claim 1 in association with a pharmaceutically acceptable carrier or diluent in claim 21, any fragment of a peptide according to claim 4, wherein said activity is stimulation of cell proliferation or angiogenesis in claim 31, any fusion peptide which comprises a first portion "having" the amino acid sequence of any fragment of a peptide according to claim 4 and a second portion , attached to the N-or C-terminus of the first portion, which comprises a sequence of amino acids not naturally contiguous to the first portion, said second portion comprising a membrane translocation sequence in claim 32, any composition comprising any fragment of a peptide according to claim 4, in association with a pharmaceutically acceptable carrier or diluent in claim 36; any peptide which is "composed of a variant of an amino acid sequence selected from the group consisting of SEQ ID NO: 1-3, said peptide having one or two conservative amino acid substitutions with respect to said amino acid sequence, wherein the peptide is capable of modulating a fibrin fragment E activity in claim 38

Applicant's arguments, filed 7/28/03, have been fully considered, but have not been found convincing

Applicant argues that an adequate written description can be achieved because (1) applicants have explicitly provided a small genus including different types of substitution at different positions and shown that all are active, (2) the description in the specification of an assay which is effective to identify other members of the genus, or (3) it would be inequitable to insist upon limitation of the claims to only the specified sequences (In re Goffe, 191 USPQ 429 (CCPA 1976).

However, the Examiner notes that the claimed invention which is drawn to a genus may be adequately described if there is a (1) sufficient description of a representative number of species, or (2) by disclosure of relevant, identifying characteristics sufficient to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention. To satisfy the disclosure of a "representative number of species" will depend on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. "Relevant, identifying characteristics" include structure or other physical and /or chemical properties, functional characteristics coupled with a known or disclosed correlation between function and structure, or a combination of such identifying characteristics sufficient to show the applicant was in possession of the claimed genus. (see Revised Guidelines for the Examination of Patent Applications Under the 35 U.S.C.112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No.4, pages 1099-1111, Friday January 5, 2001).

In the instant case, however, there is no described or art-recognized correlation or relationship between the structure of the invention, the SEQ ID NO: 1-3 and their modulating a fibrin

fragment E activity, the feature deemed essential to the instant invention. Therefore, one of skill in the art would not envisage, based on the instant disclosure, the claimed genus of peptide composed of SEQ ID NO: 1-3, fragments and variants thereof, wherein the variant has one or two conservative amino acid substitutions which retain thethe features essential to the instant invention.

The description of the peptides of SEQ ID NO:1-4 polypeptide in the specification of the instant application is not a representative number of embodiments to support the description of an entire genus of functionally equivalent peptides which incorporate all fragments and variants having one or two conservative substitutions. Therefore, only the peptide consisting of the amino acid sequence of SEQ ID NO: 1, 2 or 3, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph.

Applicant's arguments have been considered but are not found to be persuasive because the broad brush discussion of making and screening for variants and fragments does not constitute a disclosure of a representative number of members. No such variants were made or shown to have activity. Only the peptide of SEQ ID NO: 1-3 is disclosed. The specification's general discussion of making and screening for variants or fragments constitutes an invitation to experiment by trial and error. Such does not constitute an adequate written description for the claimed variants and fragments.

13. No claim is allowed.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 872-9307.

Maher Haddad, Ph.D.
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September 30, 2003

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